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DB=PGPB,USPT; PLUR=YES; OP=AND			
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L4	brain and L3	12	L4
L3	l1 with L2	14	L3
L2	convection adj enhanced adj delivery or non-manual or pump or (infusion or osmotic) adj pump	498836	L2
L1	raav or adeno-associated adj (virus or viral)	11084	L1

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Search Results - Record(s) 1 through 10 of 10 returned.

1. 20050019927. 13 Jul 03. 27 Jan 05. DECREASING GENE EXPRESSION IN A MAMMALIAN SUBJECT IN VIVO VIA AAV-MEDIATED RNAi EXPRESSION CASSETTE TRANSFER. Hildinger, Markus, et al. 435/456; 435/375 514/44 A61K048/00 C12N015/86 C12N005/02.

2. 20040220082. 21 Jan 04. 04 Nov 04. Manipulation of neuronal ion channels. Surmeier, D. James, et al. 514/2; 435/368 A61K038/16 C12N005/08.

3. 20040143860. 22 Jan 04. 22 Jul 04. Novel presenilin associated membrane protein (PAMP)and uses thereof. St. George-Hyslop, Peter H., et al. 800/12; 435/226 435/320.1 435/354 435/69.1 536/23.2 A01K067/00 C07H021/04 C12N009/64.

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5. 20030050273. 28 Aug 02. 13 Mar 03. Compositions and methods for treating neurodegenerative diseases. Ozawa, Keiya, et al. 514/44; 424/93.2 435/235.1 435/320.1 435/456 A61K048/00 C12N007/00 C12N015/861.

6. 20020141980. 21 Jun 01. 03 Oct 02. Convection-enhanced delivery of AAV vectors. Bankiewicz, Krys, et al. 424/93.21; 424/93.6 A61K048/00.

7. 20020131956. 12 Mar 02. 19 Sep 02. Adeno-associated virus vectors encoding factor VIII and methods of using the same. Walsh, Christopher E., et al. 424/93.2; 435/235.1 435/456 A61K048/00 C12N007/00 C12N015/861.

8. 20020058276. 31 Aug 01. 16 May 02. Proteins related to schizophrenia and uses thereof. St. George-Hyslop, Peter H., et al. 435/6; 424/9.2 800/3 C12Q001/68 A61K049/00 A01K067/00.

9. 6812337. 31 Mar 00; 02 Nov 04. Presenilin associated membrane protein and uses thereof. St. George-Hyslop; Peter, et al. 536/23.5; 435/325 435/69.1 435/70.1. C07H021/04 C12P021/06 C12P021/04 C12N005/00.

10. 6309634. 26 Jun 99; 30 Oct 01. Methods of treating Parkinson's disease using recombinant adeno-associated vector (rAAV). Bankiewicz; Krys, et al. 424/93.2; 424/93.6 435/235.1 435/320.1 514/44 536/23.2 536/23.5. A01N043/04 A01N063/00 C12N015/00 C12N007/00 C07H021/04.

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Terms	Documents
mm and L4	10

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     (FILE 'HOME' ENTERED AT 13:49:00 ON 14 MAR 2005)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 13:49:15 ON 14 MAR
     2005
L1         11302 S RAAV OR ADENO-ASSOCIATED(W)(VIRUS OR VIRAL)
L2        294134 S CONVECTION(W)ENHANCED(W)DELIVERY OR NON-MANUAL OR PUMP OR (OS
L3            50 S L1 AND L2
L4            32 S L3 AND BRAIN
L5          9482 S 5MM
L6             0 S L4 AND L5
L7            20 DUP REM L4 (12 DUPLICATES REMOVED)
L8             2 S MM AND L7

=> d au ti so pi ab 1-20 l7

L7   ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Kaemmerer, William F.
TI   Treatment of neurodegenerative disease through intracranial delivery of
     siRNA
SO   PCT Int. Appl., 228 pp.
     CODEN: PIXXD2
     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
PI   WO 2004047872         A2    20040610    WO 2003-US337650         20031126
     WO 2004047872         A3    20050203
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,
             NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AB   The present invention provides devices, small interfering RNA (siRNA), and
     methods for treating a neurodegenerative disorder.  A catheter is
     surgically implanted so that a discharge portion of the catheter lies
     adjacent to a predetd. infusion site in a brain, and a predetd.
     dosage of at least one substance capable of inhibiting production of at least
     one neurodegenerative protein is discharged through the discharge portion
     of the catheter.  The present invention also provides siRNA vectors, and
     methods for treating neurodegenerative disorders such as Alzheimer's
     disease, Parkinson's disease, Huntington's disease, spinocerebellar ataxia
     type 1, type 2, type 3, and/or dentatorubral-pallidoluysian atrophy.
     Thus, anti-ataxin1 siRNAs targeting the mRNA sequence at sites numbered
     945-965 and 1071-1691 are constructed and transfected into HEK293 cells at
     dosages of 0.303-0.505 pg/μg of total cellular RNA.  Quant. RT-PCR
     demonstrates that both siRNAs were effective at reducing the amount of
     ataxin1 mRNA in these cells within 48 h after transfection, and that the
     siRNA were more effective at the reduction of ataxin1 mRNA than was an
     anti-ataxin1 ribozyme.

L7   ANSWER 2 OF 20  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Dangond, Fernando; Hwang, Daehee; Gullans, Steven R.
TI   Genes showing altered patterns of expression in the central nervous system
     in multiple sclerosis and their diagnostic and therapeutic use
SO   PCT Int. Appl., 139 pp.
     CODEN: PIXXD2
     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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PI	WO 2004028339	A2	20040408	WO 2003-US29451	20030925
	WO 2004028339	A3	20040805		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004156826	A1	20040812	US 2003-670766	20030925

AB The present invention identifies a number of gene markers whose expression is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression.

L7 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

IN Kaemmerer, William F.

TI Treatment of neurodegenerative disease through intracranial delivery of siRNAs against proteins associated with the diseases

SO U.S. Pat. Appl. Publ., 206 pp., Cont.-in-part of U.S. Ser. No. 721,693.
CODEN: USXXCO

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004220132	A1	20041104	US 2004-852997	20040525
US 2004162255	A1	20040819	US 2003-721693	20031125
US 2005048641	A1	20050303	US 2004-962732	20041012

AB The present invention provides devices, small interfering RNA (siRNA), and methods for treating a neurodegenerative disorder. A catheter is surgically implanted so that a discharge portion of the catheter lies adjacent to a predetd. infusion site in a **brain**, and a predetd. dosage of at least one substance capable of inhibiting production of at least one neurodegenerative protein is discharged through the discharge portion of the catheter. The present invention also provides siRNA vectors, and methods for treating neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, spinocerebellar ataxia type 1, type 2, type 3, and/or dentatorubral-pallidoluysian atrophy. Small interfering RNAs targeting ataxin-1 mRNA that were effective in lowering concns. of ataxin 1 mRNA when applied to HEK293 cells at dosages of 0.303-0.505 pg/μg of total cellular RNA. MRNA levels dropped within 48 h and the siRNA was more effective than a ribozyme against ataxin 1 mRNA.

L7 ANSWER 4 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Sanftner L M (Reprint); Suzuki B M; Doroudchi M M; Feng L; McClelland A; Forsayeth J R; Cunningham J

TI Striatal delivery of **rAAV**-hAADC to rats with preexisting immunity to AAV

SO MOLECULAR THERAPY, (MAR 2004) Vol. 9, No. 3, pp. 403-409.
Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
ISSN: 1525-0016.

AB We tested the hypotheses that initial immunization of rats with **rAAV** might limit subsequent transduction by **rAAV**-hAADC when sterecitaxically infused into the striatum and that the level of inhibition would correlate with AAV neutralizing antibody titers. Immunohistochemical detection of AADC and analysis by stereology revealed that the control group (no immunization) had the greatest volume of

distribution of AADC (20.32 +/- 2.03 mm(3)) (+/-SD). There was a 58% decrease in spread (8.46 +/- 3.67 mm(3), P < 0.008) in the high-dose immunization group (5 x 10(10) vg **rAAV**-null). Transduction weakly correlated with preexisting titer levels of neutralizing antibody at the time of intrastriatal **rAAV**-hAADC infusion. Only rats with neutralizing antibody titers of 1: 1208 332 had significantly decreased AADC transgene expression compared to the unimmunized control group. Immunohistochemistry on serial sections for inflammatory markers including CFAP, CD11b, CD4, and CD8a revealed normal morphology and no cellular infiltration, suggesting little immune reaction in the CNS. We conclude that **rAAV** vectors can transduce **brain** tissue in the context of preexisting immunity, but that efficiency of transduction declines significantly in the presence of very high titers of neutralizing antibodies. These results have important implications for gene therapy for CNS disorders.

L7 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
IN Ozawa, Keiya; Muramatsu, Shin-ichi
TI Use of **adeno-associated virus** vectors for delivery of mammalian glial-derived neutrophic factor genes for treatment of neurodegenerative diseases
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003018821	A2	20030306	WO 2002-JP8761	20020829
WO 2003018821	A3	20031030		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003050273	A1	20030313	US 2002-230875	20020828
EP 1421199	A2	20040526	EP 2002-760784	20020829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005501127	T2	20050113	JP 2003-523668	20020829

AB Compns. and methods for treating subjects with preexisting neuronal damage are disclosed. The compns. and methods use **adeno-assocd** . **virus** (AAV)-based gene delivery systems for delivering glial cell line-derived neutrophic factor (GDNF) to subjects with neurodegenerative conditions such as Parkinson's disease.

L7 ANSWER 6 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Wang C; Wang C M; Clark K R; Sferra T J (Reprint)
TI Recombinant AAV serotype 1 transduction efficiency and tropism in the murine **brain**
SO GENE THERAPY, (AUG 2003) Vol. 10, No. 17, pp. 1528-1534.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.
ISSN: 0969-7128.
AB Recombinant **adeno-associated virus** serotype 2 (rAAV2) vectors have shown promise as therapeutic agents for neurologic disorders. However, intracerebral administration of this vector leads to preferential transduction of neurons and a restricted region of transgene expression. The recently developed **rAAV** vectors based upon nonserotype 2 viruses have the potential to overcome these

limitations. Therefore, we directly compared a **rAAV** type 1 to a type 2 vector in the murine **brain**. The vectors were engineered to carry identical genomes (AAV2 terminal repeat elements flanking an enhanced green fluorescent protein expression cassette) and were administered by stereotaxic-guided intracerebral injection. We found that the rAAV1 vector (rAAV1-GFP) had a 13- to 35-fold greater transduction efficiency than that of the rAAV2 vector (rAAV2-GFP). Also, rAAV1-transduced cells were observed at a greater distance from the injection site than rAAV2-transduced cells. Neurons were the predominant cell type transduced by both vector types. However, in contrast to rAAV2-GFP, rAAV1-GFP was capable of transducing glial and ependymal cells. Thus, rAAV1-based vectors have biologic properties within the **brain** distinct from that of rAAV2. These differences might be capitalized upon to develop novel gene transfer strategies for neurologic disorders.

L7 ANSWER 7 OF 20 MEDLINE on STN

AU Eisch Amelia J; Bolanos Carlos A; de Wit Joris; Simonak Ryan D; Pudiak Cindy M; Barrot Michel; Verhaagen Joost; Nestler Eric J

TI **Brain**-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression.

SO Biological psychiatry, (2003 Nov 15) 54 (10) 994-1005. Journal code: 0213264. ISSN: 0006-3223.

AB BACKGROUND: Previous work has shown that **brain**-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase receptor B (TrkB), are involved in appetitive behavior. Here we show that BDNF in the ventral tegmental area-nucleus accumbens (VTA-NAc) pathway is also involved in the development of a depression-like phenotype. METHODS: **Brain**-derived neurotrophic factor signaling in the VTA-NAc pathway was altered in two complementary ways. One group of rats received intra-VTA infusion of vehicle or BDNF for 1 week. A second group of rats received intra-NAc injections of vehicle or **adeno-associated viral** vectors encoding full-length (TrkB.FL) or truncated (TrkB.T1) TrkB; the latter is kinase deficient and serves as a dominant-negative receptor. Rats were examined in the forced swim test and other behavioral tests. RESULTS: Intra-VTA infusions of BDNF resulted in 57% shorter latency to immobility relative to control animals, a depression-like effect. Intra-NAc injections of TrkB.T1 resulted in and almost fivefold longer latency to immobility relative to TrkB.FL and control animals, an antidepressant-like effect. No effect on anxiety-like behaviors or locomotion was seen. CONCLUSIONS: These data suggest that BDNF action in the VTA-NAc pathway might be related to development of a depression-like phenotype. This interpretation is intriguing in that it suggests a role for BDNF in the VTA-NAc that is opposite of the proposed role for BDNF in the hippocampus.

L7 ANSWER 8 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Xu, Y. [Reprint Author]; Wang, L.; Uy, M. I.; Li, J.; Wang, B.; Zhou, L.; Xiao, X.

TI Widespread gene delivery and expression in adult mouse **brain** by recombinant **adeno - associated virus** for potential gene therapy of ischemic injuries in selective vulnerable regions.

SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 861.9. http://sfn.scholarone.com. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

AB Many disseminated neurological disorders are potentially manageable by gene therapy. Widespread somatic gene transfer in adult CNS by systemic delivery and without irradiation has not been documented. We report here the successful use of recombinant **adeno-associated virus** serotype-5 (rAAV5) vectors for widespread delivery of the beta-galactosidase (beta-gal) reporter expression cassette and

brain-derived neurotrophic factor (BDNF) into the adult mouse **brain**.Intraventricular microinjection was performed using a microprocessor-driven syringe **pump** at a rate comparable to the flow of the cerebral spinal fluid. Nine to 35 days after injection, widespread beta-gal expression can be found in the hippocampal CA1, CA3, dentate gyrus, subventricular zone, indusium griseum, lateral entorhinal cortex, and septal regions. The beta-gal positive cells were detected in a wide span of 5.74 mm in the rostral-caudal direction. The pattern of BDNF expression is very similar. A slight shift of the injection site to the more posterior location extended the transgene expression to thalamus, hypothalamus, and dorsal lateral geniculate regions. Quantitative analysis suggests that the percentage of the infected cells varies with **brain** regions and anatomic structures. Immunohistostaining and co-localization show that most of the positively stained cells are neurons.We conclude that 1) widespread gene delivery to the central nervous system is possible with rAAV5; 2) the transgene expressions are predominantly in neurons; 3) the transgene distribution pattern depends on the injection site; and 4) there is a significant level of expression in the contralateral side of the injection, suggesting a transgene migration to locations remote from the injection site.

L7 ANSWER 9 OF 20 MEDLINE on STN DUPLICATE 1
AU Fisher Robert S; Ho Jet
TI Potential new methods for antiepileptic drug delivery.
SO CNS drugs, (2002) 16 (9) 579-93. Ref: 125
Journal code: 9431220. ISSN: 1172-7047.
AB Use of novel drug delivery methods could enhance the efficacy and reduce the toxicity of antiepileptic drugs (AEDs). Slow-release oral forms of medication or depot drugs such as skin patches might improve compliance and therefore seizure control. In emergency situations, administration via rectal, nasal or buccal mucosa can deliver the drug more quickly than can oral administration. Slow-release oral forms and rectal forms of AEDs are already approved for use, nasal and buccal administration is currently off-label and skin patches for AEDs are an attractive but currently hypothetical option. Therapies under development may result in the delivery of AEDs directly to the regions of the **brain** involved in seizures. Experimental protocols are underway to allow continuous infusion of potent excitatory amino acid antagonists into the CSF. In experiments with animal models of epilepsy, AEDs have been delivered successfully to seizure foci in the **brain** by programmed **infusion pumps**, acting in response to computerised EEG seizure detection. Inactive prodrugs can be given systemically and activated at the site of the seizure focus by locally released compounds. One such drug under development is DP-VPA (or DP16), which is cleaved to valproic acid (sodium valproate) by phospholipases at the seizure focus. Liposomes and nanoparticles are engineered micro-reservoirs of a drug, with attached antibodies or receptor-specific binding agents designed to target the particles to a specific region of the body. Liposomes in theory could deliver a high concentration of an AED to a seizure focus. Penetration of the blood-**brain** barrier can be accomplished by linking large particles to iron transferrin or biological toxins that can cross the barrier. In the near future, it is likely that cell transplants that generate neurotransmitters and neuromodulators will accomplish renewable endogenous drug delivery. However, the survival and viability of transplanted cells have yet to be demonstrated in the clinical setting. Gene therapy also may play a role in local drug delivery with the use of adenovirus, **adeno-associated virus**, herpesvirus or other delivery vectors to induce **brain** cells to produce local modulatory substances. New delivery systems should significantly improve the therapeutic/toxic ratio of AEDs.

L7 ANSWER 10 OF 20 MEDLINE on STN
AU Zhang Y; Wilsey J T; Frase C D; Matheny M M; Bender B S; Zolotukhin S;

Scarpace P J
TI Peripheral but not central leptin prevents the immunosuppression associated with hypoleptinemia in rats.
SO Journal of endocrinology, (2002 Sep) 174 (3) 455-61.
Journal code: 0375363. ISSN: 0022-0795.
AB Leptin is a peripheral immunoenhancing reagent that directly activates splenic lymphocytes in mice. We found that a 48 h fast in rats resulted in a decrease in serum leptin that was accompanied by a lower delayed-type hypersensitivity (DTH) response. Peripheral leptin replacement completely restored this response in fasted animals. We employed a recombinant **adeno-associated virus** (**rAAV**) system to deliver leptin gene directly into rat **brain** to assess the effect of sustained long-term central expression of leptin on immune responses. The **rAAV**-leptin rats had elevated central leptin over the 60 day duration of the experiment, whereas body fat and circulating leptin fell to near zero levels. The DTH response was significantly reduced by 10-20% in rats receiving **rAAV**-leptin compared with the control rats, and the difference was maintained for over 50 h. When the rats undergoing **rAAV**-leptin gene therapy were given either murine recombinant leptin or PBS s.c., rats receiving leptin had a 17% higher DTH response than rats receiving PBS. The isolated splenocytes from the former group also proliferated 34% more in vitro in response to the mitogen concanavalin A as compared with the latter group. These results suggest that peripheral leptin has a dominant role in maintaining T-cell-mediated immune responses in rats, and central leptin is unable to compensate for the immunosuppression associated with peripheral hypoleptinemia. Furthermore, preservation of normal cell-mediated immune responses does not require fat tissue as along as serum leptin levels are maintained.

L7 ANSWER 11 OF 20 MEDLINE on STN DUPLICATE 2
AU Blomer Ulrike; Ganser Arnold; Scherr Michaela
TI Invasive drug delivery.
SO Advances in experimental medicine and biology, (2002) 513 431-51. Ref: 150
Journal code: 0121103. ISSN: 0065-2598.
AB The central nervous system is a very attractive target for new therapeutic strategies since many genes involved in neurological diseases are known and often only local low level gene expression is required. However, as the blood **brain** barrier on one hand prevents some therapeutic agents given systematically from exerting their activity in the CNS, it also provides an immune privileged environment. Neurosurgical technology meanwhile allows the access of nearly every single centre of the CNS and provides the surgical tool for direct gene delivery via minimal invasive surgical approaches to the **brain**. Successful therapy of the central nervous system requires new tools for delivery of therapeutics in vitro and in vivo (Fig. 1). The application of therapeutic proteins via **pumps** into the CSF was shown to be only of limited value since the protein mostly is not sufficiently transported within the tissue and the half life of proteins limits the therapeutic success. Direct gene delivery into the host cell has been a main strategy for years, and in the beginning the direct DNA delivery or encapsulation in liposomes or other artificial encapsulation have been applied with different success. For several years the most promising tools have been vectors based on viruses. Viruses are able to use the host cell machinery for protein synthesis, and some of them are able to stably insert into the host cell genome and provide long term transgene expression as long as the cell is alive. The increasing knowledge of viruses and their live cycle promoted the development of viral vectors that function like a shuttle to the cell, with a single round of infection either integrating or transiently expressing the transgene. Viral vectors have proven to be one of the most efficient and stable transgene shuttle into the cell and have gained increasing importance. The limitations of some viral vectors like the

adenoviral vector and **adeno-associated viral**
vector have been improved by new constructs like HIV-1 based lentiviral vectors. The immune response caused by expression of viral proteins, or the inability of some viral vectors like the retroviral vector to infect only dividing cells have been overcome by these new constructs. Lentiviral vectors allow an efficient and stable transgene expression over years in vivo without effecting transgene expression or immune response. In this Chapter we will describe synthetic vectors, give an overview of the most common viral vectors and focus our attention on lentiviral vectors, since we consider them to be the most efficient tool for gene delivery in the CNS.

L7 ANSWER 12 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Ruitenberg, Marc J.; Eggers, Ruben; Boer, Gerard J.; Verhaagen, Joost [Reprint Author]

TI **Adeno-associated viral** vectors as agents for gene delivery: Application in disorders and trauma of the central nervous system.

SO Methods (Orlando), (October 2002) Vol. 28, No. 2, pp. 182-194. print. ISSN: 1046-2023 (ISSN print).

AB The use of viral vectors as agents for gene delivery provides a direct approach to manipulate gene expression in the mammalian central nervous system (CNS). The present article describes in detail the methodology for the injection of viral vectors, in particular **adeno-associated virus** (AAV) vectors, into the adult rat **brain** and spinal cord to obtain reproducible and successful transduction of neural tissue. Surgical and injection procedures are based on the extensive experience of our laboratory to deliver viral vectors to the adult rat CNS and have been optimized over the years. First, a brief overview is presented on the use and potential of viral vectors to treat neurological disorders or trauma of the CNS. Next, methods to deliver AAV vectors to the rat **brain** and spinal cord are described in great detail with the intent of providing a practical guide to potential users. Finally, some data on the experimental outcomes following AAV vector-mediated gene transfer to the adult rat CNS are presented as is a brief discussion on both the advantages and limitations of AAV vectors as tools for somatic gene transfer.

L7 ANSWER 13 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Klein R L (Reprint); Hamby M E; Gong Y; Hirko A C; Wang S; Hughes J A; King M A; Meyer E M

TI Dose and promoter effects of **adeno-associated viral** vector for green fluorescent protein expression in the rat **brain**

SO EXPERIMENTAL NEUROLOGY, (JUL 2002) Vol. 176, No. 1, pp. 66-74. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 0014-4886.

AB Previous studies demonstrated that the rat neuron-specific enolase (NSE) promoter is effective for transgene expression in the **brain** in a variety of **adeno-associated virus**-2 vectors. This study evaluated the dose response and longer time course of this promoter and compared it to two cytomegalovirus/chicken beta-actin hybrid (CBA) promoter-based systems. NSE promoter-driven green fluorescent protein (GFP)-expressing neurons were found at doses as low as 107 particles, with expression increasing in a dose-dependent manner over a 3.3-log range. Bicistronic expression of GFP via an internal ribosome entry site coupled to the NSE promoter was also dose dependent, although the potency was decreased by 3.4-fold. The number of GFP-expressing neurons was stable for at least 25 months. The CBA promoter increased the numbers of GFP-expressing cells versus the NSE promoter, although the

expression pattern remained neuronal and persisted for at least 18 months. The CBA promoter permitted detection of cells distal to the injection site that had retrogradely transported the vector from their terminal areas. Incorporating the woodchuck hepatitis virus post-transcriptional regulatory element (WPRE) into a CBA promoter vector induced greater expression levels in the hippocampus, as measured by stereological estimates of cell numbers and by Western blots, which demonstrated an 11-fold increase. Incorporation of the WPRE also improved transgene expression in primary neuronal cultures. The increased efficiency obtained with vector elements such as the CBA promoter and the WPRE may enhance the ability to genetically modify larger portions of the **brain** while requiring smaller doses and volumes. (C) 2002 Elsevier Science (USA).

L7 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
IN Mandel, Ronald J.; Leff, Stuart E.
TI Method of controlling L-dopa production and of treating dopamine deficiency
SO U.S., 13 pp.
CODEN: USXXAM

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6319905	B1	20011120	US 1999-314790	19990519

AB The present invention provides an effective approach to achieve the tightly modulated production of L-DOPA and/or dopamine at a preselected target location in the **brain** of a mammal by combining gene therapy approaches to supply a key enzyme in the synthesis of L-DOPA such as tyrosine hydroxylase, and novel drug delivery modalities to administer a uniform level of a modulator of the activity of such key enzyme. The fine-tuned administration of the modulator establishes continuously uniform levels of modulator which in turn allow the effective modulation of L-DOPA and/or dopamine levels at a preselected target location in the **brain** of the mammal.

L7 ANSWER 15 OF 20 MEDLINE on STN DUPLICATE 3
AU Nguyen J B; Sanchez-Pernaute R; Cunningham J; Bankiewicz K S
TI **Convection-enhanced delivery** of AAV-2 combined with heparin increases TK gene transfer in the rat **brain**
.
SO Neuroreport, (2001 Jul 3) 12 (9) 1961-4.
Journal code: 9100935. ISSN: 0959-4965.
AB **Adeno-associated virus** type2 (AAV-2) binds to heparan-sulfate proteoglycans on the cell surface. In vivo, attachment of viral particles to cells adjacent to the injection tract limits the distribution of AAV-2 when infused into the CNS parenchyma and heparin co-infusion might decrease the binding of AAV-2 particles to cells in the vicinity of the infusion tract. We have previously shown that heparin co-infusion combined with **convection enhanced delivery** enhances distribution of the GDNF family trophic factors (heparin-binding proteins) in the rat **brain**. In this work we show that heparin co-infusion significantly increases the volume of distribution of AAV-2 as demonstrated by immunoreactivity to the transgene product 6 days after infusion into the rat striatum.

L7 ANSWER 16 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Aebischer, Patrick [Reprint author]; Ridet, Jean-Luc
TI Recombinant proteins for neurodegenerative diseases: The delivery issue.
SO Trends in Neurosciences, (September, 2001) Vol. 24, No. 9, pp. 533-540. print.
CODEN: TNSCDR. ISSN: 0166-2236.
AB Tackling neurodegenerative diseases represents a formidable challenge for our ageing society. Recently, major achievements have been made in understanding the molecular mechanisms responsible for such diseases, and,

simultaneously, numerous proteins such as neurotrophic factors, anti-apoptotic or anti-oxidant have been identified as potential therapeutic agents. Although many neurotrophic factors have been tested on individuals suffering from various neurodegenerative disorders, to date none has shown efficacy. Inadequate protein delivery is believed to be part of the problem. Recent improvements in **pump** technology, as well as in cell and gene therapy, are providing innovative ways to allow localized, regulatable delivery of proteins in **brain** parenchyma, opening new avenues for clinical trials in the not so distant future.

L7 ANSWER 17 OF 20 MEDLINE on STN DUPLICATE 4
AU Cunningham J; Oiwa Y; Nagy D; Podsakoff G; Colosi P; Bankiewicz K S
TI Distribution of AAV-TK following intracranial **convection-enhanced delivery** into rats.
SO Cell transplantation, (2000 Sep-Oct) 9 (5) 585-94.
Journal code: 9208854. ISSN: 0963-6897.
AB **Adeno-associated virus** (AAV)-based vectors are being tested in animal models as viable treatments for glioma and neurodegenerative disease and could potentially be employed to target a variety of central nervous system disorders. The relationship between dose of injected vector and its resulting distribution in **brain** tissue has not been previously reported nor has the most efficient method of delivery been determined. Here we report that **convection-enhanced delivery** (CED) of 2.5 x 10(8), 2.5 x 10(9), or 2.5 x 10(10) particles of AAV-thymidine kinase (AAV-TK) into rat **brain** revealed a clear dose response. In the high-dose group, a volume of 300 mm3 of **brain** tissue was partially transduced. Results showed that **infusion pump** and subcutaneous **osmotic pumps** were both capable of delivering vector via CED and that total particle number was the most important determining factor in obtaining efficient expression. Results further showed differences in histopathology between the delivery groups. While administration of vector using **infusion pump** had relatively benign effects, the use of **osmotic pumps** resulted in notable toxicity to the surrounding **brain** tissue. To determine tissue distribution of vector following intracranial delivery, PCR analysis was performed on tissues from rats that received high doses of AAV-TK. Three weeks following CED, vector could be detected in both hemispheres of the **brain**, spinal cord, spleen, and kidney.

L7 ANSWER 18 OF 20 MEDLINE on STN DUPLICATE 5
AU Bankiewicz K S; Eberling J L; Kohutnicka M; Jagust W; Pivirotto P; Bringas J; Cunningham J; Budinger T F; Harvey-White J
TI **Convection-enhanced delivery** of AAV vector in parkinsonian monkeys; in vivo detection of gene expression and restoration of dopaminergic function using pro-drug approach.
SO Experimental neurology, (2000 Jul) 164 (1) 2-14.
Journal code: 0370712. ISSN: 0014-4886.
AB Using an approach that combines gene therapy with aromatic l-amino acid decarboxylase (AADC) gene and a pro-drug (l-dopa), dopamine, the neurotransmitter involved in Parkinson's disease, can be synthesized and regulated. Striatal neurons infected with the AADC gene by an **adeno-associated viral** vector can convert peripheral l-dopa to dopamine and may therefore provide a buffer for unmetabolized l-dopa. This approach to treating Parkinson's disease may reduce the need for l-dopa/carbidopa, thus providing a better clinical response with fewer side effects. In addition, the imbalance in dopamine production between the nigrostriatal and mesolimbic dopaminergic systems can be corrected by using AADC gene delivery to the striatum. We have also demonstrated that a fundamental obstacle in the gene therapy approach to the central nervous system, i.e., the ability to deliver viral vectors in sufficient quantities to the whole **brain**, can be overcome by

using **convection-enhanced delivery**.
Finally, this study demonstrates that positron emission tomography and the AADC tracer, 6-[(18)F]fluoro-l-m-tyrosine, can be used to monitor gene therapy in vivo. Our therapeutic approach has the potential to restore dopamine production, even late in the disease process, at levels that can be maintained during continued nigrostriatal degeneration.

L7 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
IN Bankiewicz, Krys; Cunningham, Janet; Eberling, Jamie L.
TI **Convection-enhanced delivery** of AAV vectors to the CNS and therapeutic use thereof
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9961066	A2	19991202	WO 1999-US11687	19990526
WO 9961066	A3	20000504		
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2329259	AA	19991202	CA 1999-2329259	19990526
CA 2329259	C	20030805		
CA 2425820	AA	19991202	CA 1999-2425820	19990526
EP 1080202	A2	20010307	EP 1999-925906	19990526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6309634	B1	20011030	US 1999-320171	19990526
JP 2002516295	T2	20020604	JP 2000-550525	19990526
US 2002141980	A1	20021003	US 2001-887854	20010621

AB Methods of delivering viral vectors, particularly recombinant adeno-associated virions, to the CNS are provided. Also provided are methods of treating Parkinson's Disease.

L7 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
IN Lalwani, Anil; Schindler, Robert A.
TI Transformation and gene therapy of cells of the inner ear
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9800014	A1	19980108	WO 1997-US11602	19970627
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9735915	A1	19980121	AU 1997-35915	19970627

AB Compns. and methods are disclosed for transformation of cells of the inner ear and treatment of conditions of the inner ear using such methods. More specifically, cells of an inner ear of a subject are genetically altered to operatively incorporate a nucleotide sequence which expresses a gene product of interest (e.g., a therapeutic gene product). Preferably, the inner ear cell into which the DNA of interest is introduced and expressed is a cell of the cochlea, more preferably a cell of the spiral ligament, spiral limbus, stria vascularis, organ of Corti, spiral ganglion, and/or Reissner's membrane, and/or an auditory hair cell. The DNA of interest, preferably present within an **adeno-assocd**.
viral vector, is introduced through a cannula inserted in the round or oval window and in communication with the perilymph or endolymph.

Preferably, introduction of the DNA of interest is accomplished using an osmotic minipump.

Day : Monday
Date: 3/14/2005

Time: 13:44:16

PALM INTRANET

Inventor Name Search Result

Your Search was:

Last Name = BANKIEWICZ
First Name = KRYS

Application#	Patent#	Status	Date Filed	Title	Inventor Name
09320171	6309634	150	05/26/1999	METHODS OF TREATING PARKINSON'S DISEASE USING RECOMBINANT ADENO-ASSOCIATED VECTOR(RAAV)	BANKIEWICZ, KRYS
09887854	Not Issued	071	06/21/2001	METHODS OF TREATING PARKINSON'S DISEASE USING VIRAL VECTORS	BANKIEWICZ, KRYS
09999203	Not Issued	041	11/30/2001	METHODS OF INCREASING DISTRIBUTION OF THERAPEUTIC AGENTS	BANKIEWICZ, KRYS
10132681	Not Issued	061	04/25/2002	METHODS OF INCREASING DISTRIBUTION OF NUCLEIC ACIDS	BANKIEWICZ, KRYS
60086949	Not Issued	159	05/27/1998	DOSAGE AND DISTRIBUTION STUDY OF AAV-TK FOLLOWING INTRACRANIAL DELIVERY INTO RATS	BANKIEWICZ, KRYS
60250286	Not Issued	159	11/30/2000	METHODS OF INCREASING DISTRIBUTION OF THERAPEUTIC AGENTS	BANKIEWICZ, KRYS
60286308	Not Issued	159	04/25/2001	METHODS OF INCREASING DISTRIBUTION OF NUCLEIC ACIDS	BANKIEWICZ, KRYS
60134748	Not Issued	159	05/18/1999	CONVECTION-ENHANCED DELIVERY OF AAV-AADC VIRAL VECTOR RESTORES DOPAMINERGIC FUNCTION IN PARKINSONIAN MONKEYS	BANKIEWICZ, KRYS S.

Inventor Search Completed: No Records to Display.

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